19 Japan Patent Office (JP)

12 Kokai Patent Gazette (A)

11 Document Number H2-49715

43 Publication Date February 20, 1990

51 Int.Cl.[5] Identification Code Intrabureau Number

A 61 K 7/00 X 7306-4C

C 7306-4C

Request for Examination Not Requested

Number of Claims 1

(5 Pages Total)

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54 Title of the Invention Beautifying Agent

21 Application Number H1-70797

22 Application Date March 22, 1989

Priority Claims 32 May 9, 1988

33 Japan (JP)

31 Patent Application S63-113286

72 Inventor Torihara Masahiro
2-28-bango Kurashiki-cho Nakajo-cho
Kita-kanbara-gun Niigata-ken
within Kurare, K.K.

72 Inventor Tamai Miyuki
2-28-bango Kurashiki-cho Nakajo-cho
Kita-kanbara-gun Niigata-ken
within Kurare, K.K.

72 Inventor Shiono Takayoshi

Reference AJ translation

2045-1 Sakazu Kurashiki-shi Okayama-ken
within Kurare, K.K.

72 Inventor Tasaka Kenji
146-11 Manbai Okayama-shi Okayama-ken

71 Applicant Kurare, K.K.
1621-banchi Sakazu Kurashiki-shi Okayama-ken

74 Agent Attorney Honda Katashi

Specifications

[omission: about 1/3 of the first page of Japanese text is covered by a small sheet with the abstract in English]

The activity of tyrosinase carries out production such as melanocyte [illegible; probably: dispersing] hormones and ultraviolet light in the generation origination of ones like skin wrinkles and freckles and the dark melanin is formed [omission]

Vitamin C has problems for the aspects of stability, variations and discolorations which originate in the instability of ones that include a water component,

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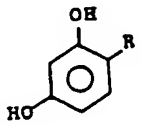
and the effect appearance is very weak for glutathione and cysteine type compounds, thus the beautifying effects are inadequate.

[Means for Solving the Problems]

These inventors, in the actual conditions such as this, fully realized the completion of this invention through the results of performing earnest research with the main objective of tyrosinase

activity inhibitors by considering the production origination of melanogenesis with the development of excellent beautifying agents with excellent effects and the appearance of ones with tyrosinase activity inhibiting effects that are extremely exceptional with the said realization of resorcinol derivatives.

Thus, this invention offers beautifying agents containing resorcinol derivatives that are represented by General Formula (1), as the effective ingredient:



...1

(In the formula, R represents straight chain alkyls of 2~12 carbon number with the substitution of 1 of the hydrogen atoms with a methyl group being desired)

The above-mentioned General Formula (1) includes ones like ethyl groups, propyl groups, butyl groups, pentyl groups, hexyl groups, heptyl groups, octyl groups, nonyl groups, decyl groups, undecyl groups and dodecyl groups as the unsubstituted straight chain alkyl groups of 2~12 carbon number represent by R. 1 of the hydrogen groups being substituted by a methyl group for these straight chain alkyl groups is desired and ones like isopropyl groups, isobutyl groups, isoamyl groups and 2-methylhexyl groups are included as concrete examples. R being an isoamyl group is a particularly desirable example.

The resorcinol derivatives which are represented by General Formula (1) are well known compounds and, for example, can be easily obtained by methods which prepare condensation products with zinc amalgams/hydrochloric acid during the condensation of carboxylic acid and resorcinol in the presence of zinc chloride (*Lille. J. Bitter, LA. Peiner. V, [illegible].Nauch-Issled.Inst. slantsov 1969,No 18, 127*), or methods with the obtainment by reactions at high temperatures of 200~400°C using alkyl alcohols corresponding to the resorcinols and alumina catalysts (British Patent No. 1,581.428).

The mixture proportions of resorcinol derivatives which are represented by General Formula (1) are 0.01 weight%~15 weight% for the cosmetic composition total weight and 0.1~10 weight% is particularly desirable for the amount.

The beautifying agents of this invention can be used along with cosmetic bases. Cosmetic base compositions are fine when there are base compositions which are commonly used for beautifying cosmetics and there are not particular restrictions. Cream, soft ointment, milky cream, toilet water, oil and pack are included as concrete cosmetic agents when preparing cosmetics using beautifying agents of this invention. For example, beeswax, cetyl alcohol, stearic acid, glycerin, propylene glycol, propylene glycol monostearate and polyoxyethylene cetyl ether are included as cream base compositions; oleyl alcohol, ethanol, propylene glycol, glycerin, lauryl ether, and sorbitan monolaurate are included as toilet water base compositions.

These raw materials are suitably used for beautifying agents of this invention and can be prepared as suitable forms of cosmetics such as creams, milky lotions and toilet waters by ordinary methods. Further, various medicinal ingredients like ultraviolet blocks that are represented by ones like fine-grain titanium oxide, ultraviolet absorbers, allantoin and placenta extract, and other thickeners, plasticizers, calamine, cosmetics, antioxidants, chelating agents and fragrances can be added in response to need for the above-mentioned ordinary cosmetic bases in beautifying agents of this invention.

[Actual Examples]

Next, the usefulness of the beautifying agents of this invention are further concretely explained.

Manufactured Example

71.85 g of thionyl chloride was dripped for 1 hour into 23.23 g of n-caproic acid at room temperature, then stirred for 5 hours.

After the completion of the reaction, the excess thionyl chloride was removed. The residue was prepared in an [illegible] solution of 150 ml of methylene and 81.77 g of zinc chloride that was cooled to 10°C; then, 26.42 g of resorcinol was gradually added and after a 30 minute reaction time,

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returned to room temperature and reacted for 8 hours. 100 ml of 5% HCl was added to the reaction solution and this was extracted 2 times with isopropyl ether.

After the removal of the isopropyl ether, the residue was

refined by column chromat[ography] (silica gel, n-hexane/ethyl acetate 3/1 (volumetric ratio)[)].

Then, 30.0 g of zinc powder with 2.50 g of mercury(II) chloride, 1.5 ml of concentrated hydrochloric acid and 38 ml of water was decanted after 5 [illegible; probably: minutes] and the aqueous solution was discarded.

Then, 20 ml of water, 45 ml of concentrated hydrochloric acid and 25 ml of toluene were [illegible] added to 14.6 g of the previously obtained n-hexyl resorcinol, and this was refluxed for 30 hours. At this time, 12.5 ml of concentrated hydrochloric acid was added about [every] 6 hours for 4 times in order to maintain the acid concentration. [This] was cooled to room temperature and separated, and the water layer was extracted 3 times with 50 ml of isopropyl ether, and the organic layer was washed with a total of 100 ml of water. The solvent was removed with an evaporator and 4.3 g of n-hexyl resorcinol was obtained as colorless needle-shaped crystals when the residue was crystallized from n-hexane.

Methyl resorcinol, ethyl resorcinol, n-propyl resorcinol, isoamyl resorcinol, n-octyl resorcinol and n-dodecyl resorcinol were synthesized by methods identical to this.

Actual Examples 1~12 (Beautifying Effects)

The inhibition of tyrosinase activity, which is imparted by the generation of melanin, by resorcinol derivatives that are represented by General Formula (1) is explained by actual examples.

Tyrosinase is a copper containing enzyme that controls melanin synthesis with tyrosine as the generating substance. This

enzyme is considered with preparation with catalysts of biosynthesis steps of dopa, dopaquinone and indole-5,6-quinone which are intermediates of melanin synthesis, and, among those, these inventors investigated the activity rate for tyrosinase activity inhibition according to the measurement of the activity which is controlled by resorcinol derivatives that are represented by General formula (1) for biosynthesis reactions of dopa (tyrosine hydroxylase) from tyrosine and dopaquinone (dopaoxydase) from dopa.

Experimental Methods

1) Measurement of Tyrosine Hydroxylation Activity

3 ml of the substrate (L-tyrosine, 1 x 10^{-4} M) solution was put into a spectrophotometer cell, and as a final concentration of 100 times the concentration of resorcinol derivatives or reference compounds, 30 μl of hydroquinone was added and mixed well. The presence of ultraviolet absorption in ones like the substrate and samples was confirmed and a reaction was initiated by adding 50 μl of tyrosinase (*Mushroom, 200 unit, Sigma* Company). Changes in absorptivity were measured at 280 nm which was the maximum absorption of L-DOPA. Tyrosine hydroxylation activity was indicated by nmol dopa/min/mg protein. The protein was measured by the *Lowry* Method.

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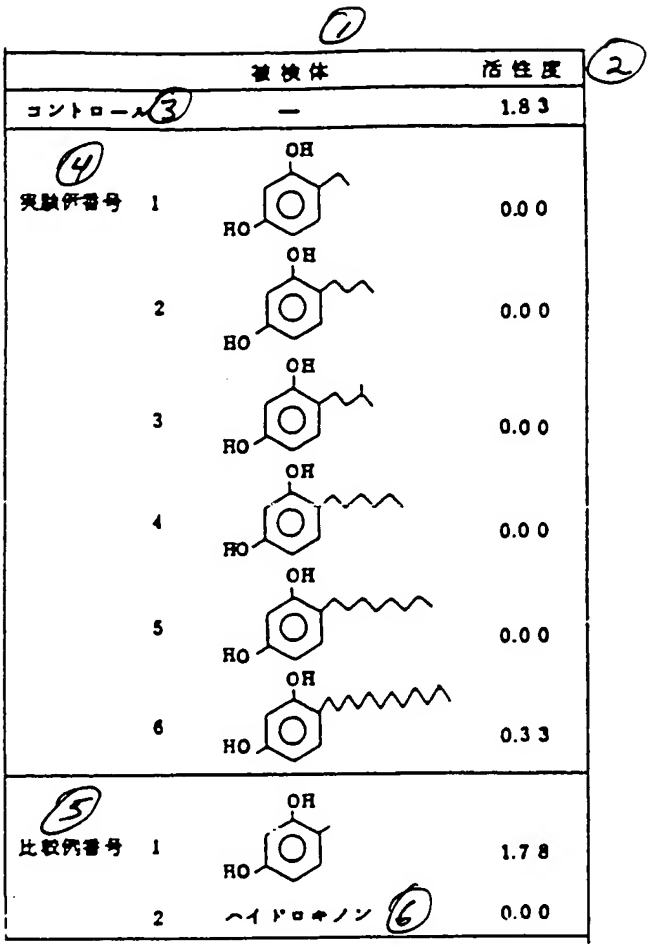

		被検体	活性度
コントロール		—	1.83
実施例番号	1		0.00
	2		0.00
	3		0.00
	4		0.00
	5		0.00
	6		0.33
比較例番号	1		1.78
	2	ハイドロキノン	0.00

[Key to Figure]

1 sample

2 activity

3 control

4 actual example number

5 reference number

6 hydroquinone

/4

2) Measurement of Dopa Oxidation Activity

L-DOPA (5×10^{-3} M) was used as the substrate, and the biosynthesized dopachrome was measured at a wavelength of 475 nm. Otherwise, there was the same method as 1) using 10 Unit[s] for tyrosinase.

The dopa oxidation activity was shown by μm dopachrome/min/mg protein.

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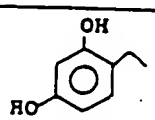
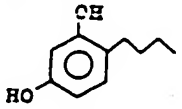
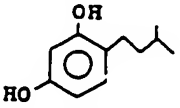
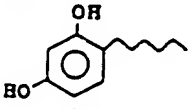
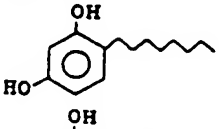
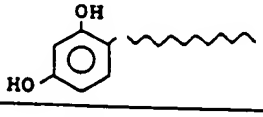
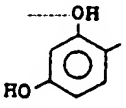
被検体 (1)		活性度 (2)
コントロール (3)	—	15.80
(4) 実験例番号 7		7.44
8		0.00
9		0.00
10		0.00
11		0.00
12		7.19
(5) 比較例番号 3		16.81
4	ヘイドロキノン (6)	26.94

1 samples

2 activity

3 control

4 actual example numbers

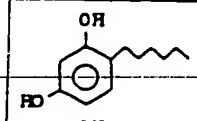
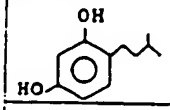
5 reference sample numbers

6 hydroquinone

Sample 1 (Color Variation Origin Properties Test)

Isoamyl resorcinol is confirmed as not having properties which originate darkening by performing Ames tests using *Salmonella typhimurium*.

For the resorcinol derivatives or reference compounds, hydroquinone was dissolved in physiological saline and this was orally dosed (p.o.), internally dosed to the peritoneal cavity (1.p.) and subcutaneously dosed (s.c.) to ddy type male mice of 10 animals in each [1] group, and the number of dead animals were counted 24 hours after dosing. The LD_{50} was calculated by the *Litchfield-wilcoxom* method based on the results. The results are shown in the following table.

(7) 化合物	LD_{50} (mg/kg) i.p.	s.c.	p.o.
	334.8	>500	>500
	2688	>500	>500
ハイドロキノン (8)	1440	338.8	489.0

[Key to the Table]

7 compound

8 hydroquinone

Next, the various compounds used for beautifying agents of

this invention are shown. The mixture amount is shown by weight%.

Compound Example 1 (Lotion)

propylene glycol	10.0
ethyl alcohol	20.0
fluid paraffin	2.0
polyoxyethylene(30) hardened castor oil	1.0
4-isoamyl resorcinol	8.0
polyethylene glycol	5.0
citric acid	0.2
sodium phosphate	0.3
allantoin	0.05
EDTA-2Na	0.05
antioxidant	0.02
fragrance	0.2
pure water	53.18

Compound Example 2 (Cream)

solid paraffin	20
stearyl alcohol	4.0
squalane	20

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fluid paraffin	6.0
glyceryl monostearate	2.5
polyoxyethylene sorbitan monostearate	2.5
ethyl alcohol	9.0
propylene glycol	8.0
4-isoamyl resorcinol	4.0
2-hydroxy-4-methoxybenzophenone	3.0
hydrophobic fine-grain titanium oxide	5.0
pure water	52.0

Compound Example 3 (Foundation)

hydrophobic fine-grain titanium oxide	7.0
triglyceride isostearate	2.0
2-octyldodecyl oleate	8.0
fluid paraffin	3.0
cetyl alcohol	5.0
[untranslatable: kyanderira; probably: calendula] wax	2.0
4-isoamyl resorcinol	5.0
polyoxyethylene(25) monostearate	2.0
sorbitan monostearate	1.0
yellow iron oxide	1.3
[illegible]	0.8
polyethylene glycol	4.0
methylparaben	0.2
fragrance	0.2
pure water	58.5

Compound Example 4 (Powder)

talc	80.0
crystalline cellulose	5.0
ultramarine	1.0
spherical calcium silicide	3.0
fine-grain titanium oxide	3.5
4-isoamyl resorcinol	3.0
squalane	4.5

Compound Example 5 (Lotion)

propylene glycol	15.0
L-menthol	0.1
ethanol	15.0
polyoxyethylene(30) hardened castor oil	0.5
anti-inflammatory agent	1.0
4-isoamyl resorcinol	1.5
triethanolamine [untranslatable: isoferura-san]	3.5
fragrance	0.3
pure water	65.1

Compound Example 6 (Pack)

polyvinyl alcohol	20.0
ethanol	20.0
[untranslatable: isoferura-san]	1.0
glycerin	5.0
fragrance	0.3
water	53.7

Compound Example 7 (Oil)

squalane	47.0
castor oil	47.0
2-ethylhexyl [untranslatable: isoferura-san]	5.0
4-isoamyl resorcinol	0.79
fragrance	0.2
antioxidant	0.01

[Results of the Invention]

The effects that inhibit the tyrosinase activity which initiates melanin production are exceptional for the beautifying agents of this invention and exceptional skin beautifying effects are produced.

Patent Applicant Kurare, K.K.

Agent Attorney Honda Katashi